

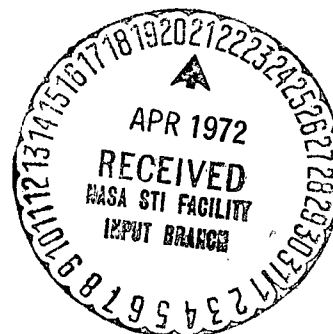
EXPERIMENTAL AND CLINICAL STUDIES IN THE TREATMENT OF ARRHYTHMIAS  
DUE TO DIGITALIS BY SODIUM CITRATE

W. Smolarz, S. Kośmider, K. Zajusz

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EXPERIMENTAL AND CLINICAL STUDIES IN THE TREATMENT OF ARRHYTHMIAS  
DUE TO DIGITALIS BY SODIUM CITRATE

W. Smolarz, S. Kośmider, K. Zajusz

ABSTRACT. Cardiac arrhythmia caused by intravenously administered digoxin (0.15 mg/kg) into dogs was terminated by subsequent intravenous injections of Na citrate (0.6-1.4 g) alone or in combination with 0.5 g KCl. The best results were obtained giving Na citrate alone, for although positive results could be obtained at a lower dosage with the administration of the 2 compounds together, ventricular flutter appeared in several cases. The intravenous infusion of Na citrate (1.2-2 g) to patients with cardiac arrhythmia due to digitalis produced normalization of the rhythm in all patients observed; however, infusions of Na citrate had to be repeated in some cases due to remission of the rhythm disturbance. The use of Na citrate in the treatment of acute digitalis toxicity was suggested.

The problem of glycoside intoxication has received increasing interest /521\* over the last few years as the use of drugs has increased which cause the excretion of potassium and other salts. The synergistic effects of calcium on glycosides and the antagonistic effects of potassium on glycosides are employed for removing the toxic effects of glycosides. In modern therapy, potassium is administered orally and by intravenous injections [3, 4, 8, 12] or Na<sub>2</sub> EDTA is administered by continuous drip infusions [2, 5, 9]. On the one hand, these drugs improve any disorder in the K gradient, and on the other hand they reduce the concentration of biologically active calcium in the area of the myofibrillae. The control function of calcium for the migration of potassium into the cells has not been explained sufficiently [1, 11].

The present experimental and clinical studies with animals investigate the changes of the Ca/K quotient in the treatment of arrhythmias due to digitalis.

Study subjects and method

The studies were conducted with:

- a) dogs which had been intoxicated with digoxin and were subsequently treated with sodium citrate or potassium chloride to remove the

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\* Numbers in the margin indicate pagination in the foreign text.

arrhythmias;

- b) heart patients with arrhythmias due to treatment with digitalis who were given sodium citrate in order to terminate the arrhythmias.

to a) The study subjects were 18 dogs of mixed breeds with body weights of 5-7 kg. The animals were anesthetized with pentothal and were intoxicated with 0.15 mg of digoxin per kg of body weight administered intravenously after a control ECG had been taken.

Usually, polymorphous extrasystoles, bigeminal pulse, nodal or chamber rhythm appeared after a few minutes which continued for several hours in the control group. Fifteen minutes after administration of digoxin, it was attempted to terminate the arrhythmias by: /522

1. Lowering the calcium level by means of 4% sodium citrate administered by intravenous injections (10 experiments).
2. Administering KCl in a continuous drip infusion and subsequent administration of sodium citrate (8 experiments).

In addition to recording the ECG curves in certain intervals, the potassium and calcium level were determined prior to administering digoxin and after termination of the arrhythmias, and the dosage needed for terminating the arrhythmias was determined.

to b) A total of 21 patients under glycoside treatment for heart insufficiencies and with symptoms of overdoses in the form of arrhythmias was administered 1.2-2.0 g sodium citrate in a physiological common salt solution by means of an intravenous continuous drip transfusion over a period of one hour. Electrocardiograms were taken before, during, and after the administration of sodium citrate and the time was recorded which passed until the arrhythmias were terminated. Simultaneously, the Ca level was determined before and after treatment according to the method developed by Kovacs [7].

### Experimental Findings

#### a) Results of the Experiments with Dogs.

## 1. Effects of Na citrate

In all 10 animal experiments, the extrasystoles or the bigeminal pulse subsided during, or immediately after, the administration of sodium citrate. The transition to a sinus rhythm could be registered on the electrocardiograph in almost all cases (Figure 1). The total dosage of Na citrate administered was 0.6 to 1.4 g. The termination of arrhythmias was present in only two cases. In the other 8 cases, arrhythmias reappeared after 5-30 minutes. The calcium level of 4.8-8.5 m liter-eq. in the serum prior to the tests was lowered by the citrate by 1.0-3.5 m liter-eq. Three animals were administered a sublethal dose of glycoside. By 523 the repeated administration of sodium citrate until tonic spasms appeared it was possible to suppress arrhythmia and to keep the animals alive. The potassium level in the serum remained unchanged before and after the tests.

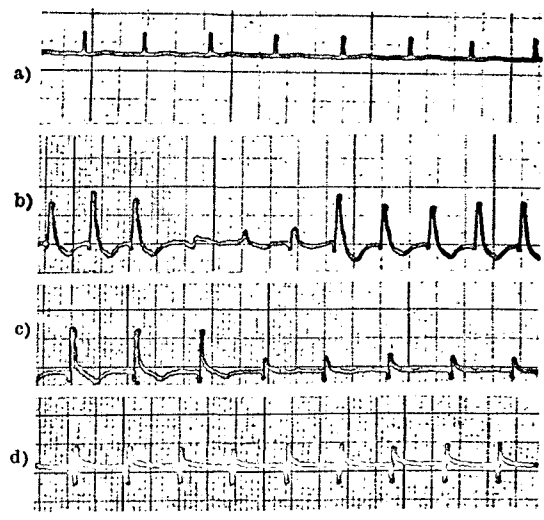


Figure 1. Effects of sodium citrate on cardiac arrhythmia in dogs due to glycosides. a) control curve, b) 15 minutes after the administration of digoxin, c) 2 minutes after sodium citrate, d) control curve after 20 minutes.

## 2. Effects of potassium chloride and sodium citrate

Eight animals were administered KCl in a continuous drip infusion (0.5 g within 1/2 hour), and then sodium citrate was administered by intravenous injection.

For this series of tests, the results were again very good (Figure 2), or sudden ventricular flutter appeared (3 animals, Figure 3). This complication could not

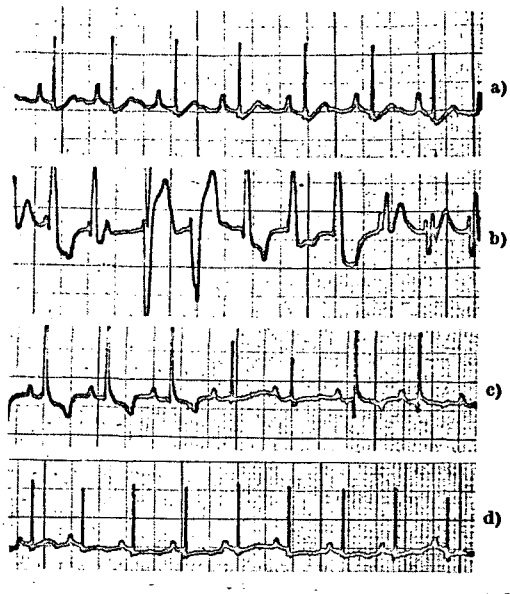


Figure 2. Effects of KCl and sodium citrate on cardiac arrhythmia in dogs due to digoxin. a) control curve, b) 15 minutes after administration of digoxin, c) 2 minutes after KCl and sodium citrate, d) control curve after 60 minutes.

be explained by the higher level of potassium or the lower level of Ca in the serum. The average dose of Na citrate administered was 0.4 g. The values for the K and Ca levels in blood before and after the test showed no significant differences.

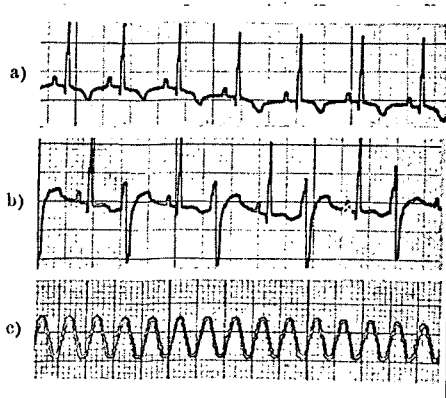


Figure 3. Ventricular flutter observed in dogs after the administration of KCl and sodium citrate. a) control curve, b) 15 minutes after administration of digoxin, c) ventricular flutter after KCl and sodium citrate.

Heart patients were chosen for treatment with sodium citrate who had shown symptoms of various arrhythmias in the course of treatment with digitalis. Though it was not possible to prove a definite correlation with digitalis toxicity for each case, the patients selected were as a rule persons who had suffered heart failure and had been taking thiazide diuretics for extended periods and, therefore, showed a low level of K in their blood serum. Thus, their sensitivity to digitalis was extremely high. Before the treatment, we found the typical arrhythmia in the form of bigeminal pulse in 10 patients, the other patients showed extrasystoles of a heterotopic or nomotopic form in the ventricle. In some cases, the arrhythmias were connected with typical symptoms of dyspepsia /525

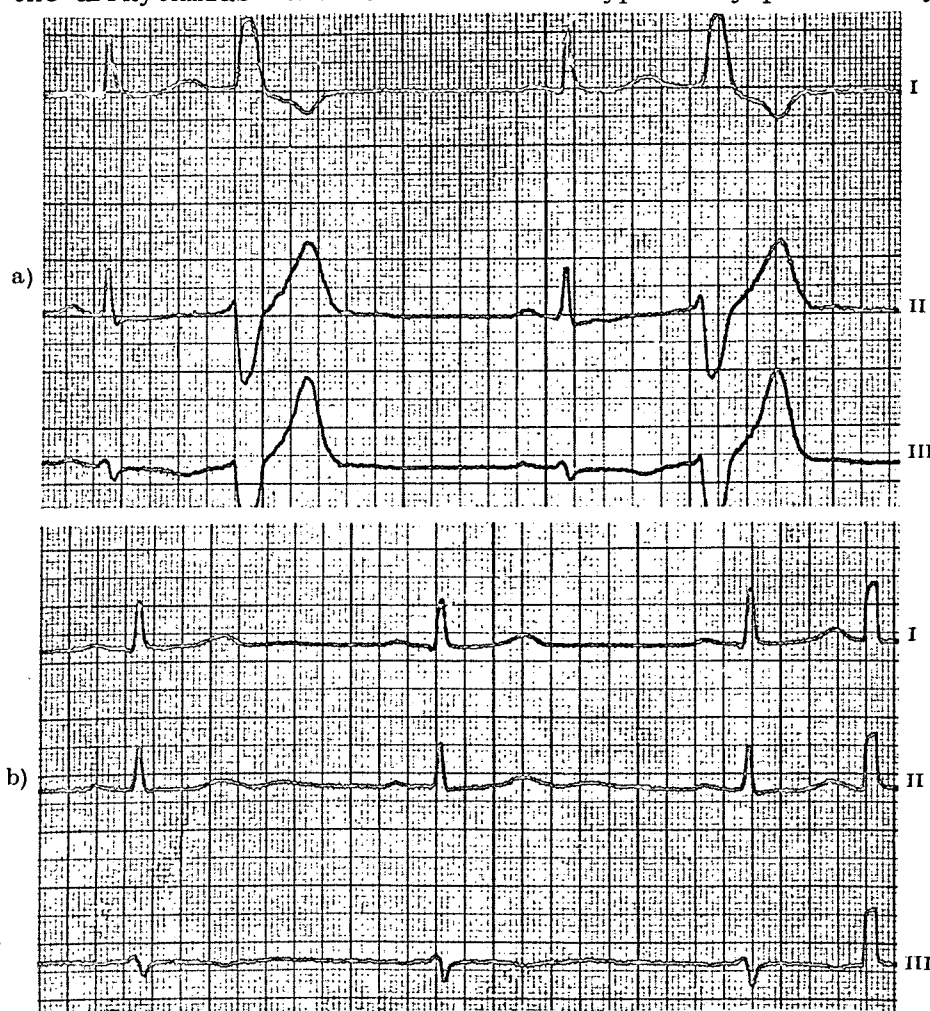


Figure 4. Effects of sodium citrate on arrhythmias in man during treatment with digitalis. a) bigeminal pulse, b) after the administration of 1.5 g Na citrate.

and further treatment with digitalis was, therefore, impossible. Sodium citrate was administered in a 5% solution with glucose in an intravenous continuous drip infusion while the patient was kept under constant observation. The dose administered was 1.2 to 2.0 g. When the rhythm normalized, the infusion was stopped. No side effects occurred. The arrhythmia disappeared in all patients observed during or after the infusion, which was confirmed by ECG (Figure 4).

When new arrhythmia appeared, which occurred in the majority of patients treated, the infusion was repeated with lower amounts of sodium citrate until the rhythm normalized again. The subjective well-being of the patients improved as a rule after arrhythmia had been normalized. The Ca level in the blood serum was 4.6-5.9 m liter-eq. prior to administration of sodium citrate and was reduced by 0.3-0.5 m liter-eq. after the infusion.

### Discussion

There are various possibilities for treating arrhythmia due to digitalis. The principle of each method is to change the concentration ratio of Ca ions to K ions [6]. Lowering the Ca level by administering sodium citrate has been proven to be a successful and safe method. It was possible to normalize arrhythmia in all cases, at least for a short period of time. So far, Na<sub>2</sub> EDTA has been used in this hospital for such treatment. But some side effects have been observed when this compound is used which prevent the application of this method on a large scale. The symptoms observed were primarily reactions similar to the effects of histamine, a strong hypotonic effect and the local irritation of veins. In our work we have not found any data that would in principle contradict the introduction of Na citrate as a compound to be used in hospitals to lower Ca levels in patients. As an additive to blood transfusions, sodium citrate is used every day for human patients. Ludbrook and Wyman [10] give a detailed description of the effects of sodium citrate when administered intravenously to animals and human patients. According to these authors, sodium citrate should not be administered to patients with liver and kidney disorders and hypothermia.

In the patients observed during our study, the treatment with sodium citrate showed good results, and no side effects were noticed. Our study showed that this method is suitable for treating life-endangering arrhythmias that occur in the course of treatment with digitalis. The successful treatment in all cases.

would indicate that sodium citrate is suitable for normalizing arrhythmias of a different origin, too. Studies in this direction would, however, require a larger group of patients because of the practical implications such a study would have today.

The combination of administering K ions and subsequently lowering the Ca ions by means of sodium citrate made it possible to normalize the heart rhythm at a considerably lower dosage of the latter compound. The sudden death of three animals due to heart failure proves, however, that sudden and adverse changes of the ratio of Ca/K ions may occur. These changes are probably too short to be measured by the customary methods of determining K and Ca levels. We, therefore, consider this method of treating digitalis toxicity as risky. /526

#### Conclusions

1. Sodium citrate is suitable for correcting arrhythmia in dogs due to digitalis.
2. The administration of K ions and sodium citrate to dogs with digitalis intoxication is considered dangerous due to rapid changes in ion ratio.
3. The treatment of arrhythmia due to digitalis with sodium citrate is considered a safe and successful method on the basis of our clinical observations.

#### Summary

Eighteen dogs were intoxicated with digoxin for inducing cardiac arrhythmias. After that, the attempt was made to remove the arrhythmias by injections of Na-citrate or KCl and Na-citrate together. The best results were obtained giving Na-citrate alone. By application of the two compounds an essential lower dose was necessary to obtain positive results. In a few cases, however, ventricular flutter appeared.

Na-citrate given intravenously to patients with cardiac arrhythmias due to digitalis has proved as a successful and undangerous method. Normalization of rhythm was obtained in all patients observed, but infusions of lower amounts of Na-citrate must have been repeated because of remissions of rhythm disturbances.

This method can be successfully used in treatment of acute digitalis toxicity often observed in clinical practice.



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